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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/276,935	03/25/99	KIDNER	S 511-125

EXAMINER	
PAK,M	
ART UNIT	PAPER NUMBER
1646	16

DATE MAILED: 10/02/01

020347
DAVID J LEVY, CORPORATE INTELLECTUAL PRO
GLAXOSMITHKLINE
FIVE MOORE DR.
PO BOX 13398
DURHAM NC 27709-3398

HM12/1002

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applic[illegible](s)
09/276,935	Kliewer et al.
Examiner	**Art Unit**
Michael Pak	1646

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Jun 27, 2001*.

2a) [ ] This action is **FINAL.** 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-24* is/are pending in the application.

4a) Of the above, claim(s) *1-9 and 11-24* is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *10* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

11) [ ] The proposed drawing correction filed on _____ is: a) approved b) disapproved.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) [X] Notice of References Cited (PTO-892)

16) [X] Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) [X] Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9, 10, 15

18) [ ] Interview Summary (PTO-413) Paper No(s).

19) [ ] Notice of Informal Patent Application (PTO-152)

20) [ ] Other

DETAILED ACTION

1. The preliminary amendment filed 20 July 2000(Paper No. 7) has been entered.

2. Applicant's election with traverse of Group IV, in Paper No. 14 is acknowledged. The traversal is on the ground(s) that the search of Group IV would encompass the subject matter of Group V with a note that Groups IV and V are classed in Class 435.it and no undue burden would be placed on the examiner. However, the groups are in different subclasses as set forth in the previous action and thus are classified separately. Furthermore, Group V encompass activation and inhibition of the receptor whereas Group IV encompass binding only. Group V requires search in receptor activation and inhibition of transcription or gene expression and constitutive activation due to mutagenesis. Whereas Group I requires search in binding kinetics and competition binding kinetics such as ligand binding affinity, equilibrium constants, dissociation constants, free energy calculation of interaction, receptor occupancy, and various equations related to affinity and occupancy such as langmuir binding isotherm, Lineweaver-Burk, Scatchard, and Eadie-Hofstee, and errors associated with the calculations.

Information Disclosure Statement

3. The information disclosure statement filed 29 August 2001 (Paper No. 15) fails to comply in part with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56 most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

JP 11-127872 is in Japanese and there is no concise explanation of the relevance.

4. The information disclosure statement filed 29 August 2001 (Paper No. 15) fails to comply in part with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because Kliewer et al.(Transcriptional ...) reference does not have the date nor the reference citation information. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements

for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

5. The letter for requesting the consideration of information disclosure statement filed 2 August 2000 (Paper No. 9) was not signed. The information disclosure statement filed 2 August 2000 (Paper No. 9) has been considered and is attached. A copy of the letter which is signed should be submitted with the next communication.

Specification

6. The disclosure is objected to because of the following informalities. Appropriate correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Page 9 contains a hyperlink which must be deleted. Please examine the specification carefully for any other hyperlinks in the text and delete the hyperlink text.

Claim Objections

7. Claim 10 is objected to because of the following informalities. Appropriate correction is required.

Claim 10 recites "hPXR" and "CYP3A4" which is an acronym which should be more clearly identified with the full name that

the acronym represents.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claim 10 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

The claims are directed to a method of using an orphan receptor with no known ligand in a test compound screening assay. The specification as filed does not disclose or provide evidence that points to a property of the claimed receptor such that another non-asserted utility would be well established. Since the function of the protein is not known because the ligand is not known, the protein lacks well established utility. The specification on page 3 disclose the asserted utility of using the PXR polypeptide in identifying assays that can be used to establish whether drugs will interact in vivo. However, without the known ligand for the PXR receptor, the development of an assay for binding of test compounds lacks substantial utility because further research to identify or reasonably confirm a "real world" context of use is required. Kliewer et al.(Cell,

1998, page 80) teach that PXR ligand is not known and is analogous to RXR receptors where all-trans retinoic acid activated the receptor at micromolar range in the same way that catatoxic steroids activate PXR, until more research found that 9-cis retinoic acid is the natural ligand of RXR. Any utility of the nucleic acid encoding the protein or other specific asserted utility is directly dependent on the function of the protein. A circular assertion of utility is created where the utility of the protein is needed to break out the circular assertion of utility. The orphan receptor polypeptide does not have well established utility because different receptors would have different functions and the skilled artisan would have to determine the function of the orphan receptor. The claimed polypeptides do not have substantial utility because the skilled artisan would need to prepare, isolate, and analyze the protein in order to determine its function and use. Therefore, the invention is not in readily available form. Instead, further experimentation of the protein itself would be required before it could be used.

Claim 10 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 U.S.C. § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recite the term "hPXR" which is not clear because the metes and bounds of the term is not clear. The term "hPXR" is recited in the claim without structural limitation, yet the specification encompasses encompass variants and fragments. It is not clear how a hPXR is to be differentiated from other PXRs such as from other animal species such as rat rPXR or their variants if the generically claimed fragments and variants overlap in structure and function.

Claim 10 recite the term "CYP3A4 gene expression" which is not clear because the metes and bounds of the term is not clear. The term "CYP3A4 gene expression" is not clear because it is not clear whether direct repeat response elements of the DNA which is common in the "CYP3A4 gene expression" is sufficient to encompass the claim limitation.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph,

as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are the measurement of CYP2A4 gene expression as stated in the preamble.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Even if claim 10 is found to have utility, it is not enabled under 35 U.S.C. 112, first paragraph.

Claim 10 method comprises using hPXR which encompasses variants and fragments without structural limitations. However, the specification does not teach how to use the variants of the PXR receptor. The working example of the species of human PXR is taught in the specification. However, one skilled in the art

cannot predictably substitute amino acid changes and retain function of the protein (Bowie et al., Science, 1990). One skilled in the art cannot predictably substitute amino acid changes in an orphan receptor because the natural ligand is not known (Kliewer et al., Cell, 1990, page 80).

Claim 10 encompasses determining a test compound effect on CYP2A4 gene expression in an assay based upon the test compound binding to the PXR receptor. However, one skilled in the art differentiate between specific and non-specific binding and a test compound which binds non-specifically would not induce CYP3A4 gene expression. Furthermore, even if the test compound binds the receptor specifically, it is well know to one skilled in the art that some compounds have no effect or are antagonists of the receptor which have no activity. Kliewer et al. teach that naturally occurring glucocorticoids including cortisol and corticosterone has no effect on PXR activity(page 77, second column, second paragraph). Furthermore, the assays do not include method steps of determining the effect of the test compound on the CY3A4 gene expression which is necessary in order to fulfill the preamble stated purpose.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under

this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claim 10 is rejected under 35 U.S.C. 102(a) as being anticipated by Kliewer et al.(Cell, 1998).

Kliewer et al. teach the binding assay with PXR and binding to pregnenolone steroids in micromolar ranges and interaction with CYP3A1 DR-3(page 77; figure 5).

16. Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Evans et al.(WO 96/22390).

Evans et al. Tteach the method of binding of 3-AEB to XOR-6 which is a nuclear receptor which binds the direct repeat DR-3 (pages 7, 9, 10, 17, 22, and 23).

Although XOR-6 is not called hPXR the claim 10 limitation without structural limitations does not exclude XOR-6 which has the functinal chracteristics and the binding assay of the method claim limitation since the DR-3 is the direct repeat response element which binds hPXR.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Pak, whose telephone number is (703) 305-7038. The examiner can normally be reached on Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Michael D. Pak

Michael D. Pak
Primary Patent Examiner
Art Unit 1646
28 September 2001

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.